THE DICK TEST

IN RELATION TO SCARLET FEVER.

by

G. W. SIMPSON,

M.A., B.Sc., M.B., Ch.B., D.P.H.

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C O N T E N T S.

PART I.

PART II.

PART I.

ETIOLOGY OF SCARLET FEVER.

The etiology of scarlet fever has been for many years past the subject of much discussion and is for the present a matter of more active investigation. Scarlet fever was recognised as early as the middle of the sixteenth century but for many years the disease was confused with measles, erysipelas, diphtheria and certain septic processes. Sydenham, who first employed the name "febris scarlatina", clearly differentiated it from measles by his full account of the disease as it appeared in London in 1675, and laid the foundation of an accurate knowledge of its special characters. Despite this valuable contribution the existing confusion continued, but, with the increasing knowledge which comes with time, scarlet fever gradually became more clearly defined as a clinical entity. Confusion, however, with diphtheria frequently occurred, even down to the times of accurate diagnosis by means of bacteriological methods. Even to-day many physicians still confound scarlet fever with diphtheria but above all with certain septic conditions of the throat, associated with erythematous rashes. Quite frequently, too, it is mistaken for other exanthemata and adventitious rashes.

In spite of these diagnostic difficulties clinical differentiation/

differentiation of scarlet fever from other infectious diseases has been possible for a long enough period of time to determine clearly its contagious nature and to permit epidemiological and clinical studies. From such studies it appears that the contagious element in scarlet fever is probably always derived from a previous case. In most instances the virus is taken directly into the mouth or nasopharynx by the inhalation of air charged with minute droplets of saliva or mucus projected from the mouth or nose of the infected individual. Another important source of contagion is the purulent discharges arising from the complications of the disease in such situations as the nose, middle ear and cervical lymph glands. Since these suppurative complications occur during convalescence it would seem that the causative virus persists in some cases in an active form for long intervals of time. This source is probably responsible for most of the cases now known as "return cases" to hospital. There is evidence also to support the view that the causative agent survives in the dry secretions in a viable and virulent form for long periods of time. Contamination, therefore, of clothing or personal articles and food utensils with infective matter may serve as a means of conveying scarlet fever. At one time the belief was prevalent that flakes of skin given off during the period of desquamation were the most/

most important vehicle of the contagion, but in these days current opinion holds that the contagious element is not present in the desquamated epithelium, unless such epithelium is contaminated with infective discharges. The rôle of the healthy carrier in spreading scarlet fever is undoubtedly gaining importance although it is difficult to determine accurately because of the uncertainty of the etiological agent. There seems, however, to be little doubt that healthy carriers do exist and Bliss (1922) was able to trace a small epidemic of scarlet fever to such a source. Another interesting means of widespread dissemination of scarlet fever is an infected milk supply and numerous undoubted outbreaks have arisen from the consumption of contaminated milk. Klein (1886) attributed an outbreak of the disease in London to streptococcal infection of the milk from a Hendon dairy, supplied by cows suffering from ulcerated udders. He succeeded in isolating a streptococcus, which he named "Streptococcus scarlatinae," both from the infected milk and from the blood of eleven scarlet fever patients who consumed the milk.

Notwithstanding the collected evidence of excellent clinical and epidemiological studies which ensured the easy recognition of typical attacks of the disease, and which furnished the essential data for quarantine regulations, the causative agent of scarlet/

scarlet fever remained unknown. Experimental studies have been published from time to time suggesting that the infective agent belongs to one or other of the principal groups of micro-organisms, such as bacteria, protozoa, and the so-called ultramicroscopic or filterable viruses. The evidence offered in favour of the protozoan origin of scarlet fever has never stood the test of close scrutiny. The belief that scarlet fever is due to an unknown virus of filterable character was widely accepted and is the usual etiology assigned in text books, although no real evidence has ever been produced.

As a bacterial cause the streptococcus has aroused much interest during the many years that investigators have searched for the cause of scarlet fever. The constant relationship to this disease of this organism has become more and more significant. Loeffler (1884) first observed the streptococcus in the throats of severe cases of scarlet fever. It was about this time (1886) that Klein attributed the milk-borne epidemic of scarlet fever to the "Streptococcus scarlatinae". These early observations of the frequent relationship of the streptococcus to scarlet fever or scarlatina were soon confirmed by many bacteriologists in different parts of the world. They noted that streptococci were very abundant in the throats of individuals acutely ill with scarlatina.

Baginsky/

Baginsky and Sommerfeld (1900) reported the constant presence of streptococcus in the throat during the characteristic angina in seven hundred cases of scarlet fever. They also found this organism frequently in the blood and internal organs of patients dying of the disease. In addition, the organism has also been proved to be the most frequent cause of the septic complications of the disease.

This widespread and more or less constant association of the streptococcus with scarlatina led some observers to the opinion that the streptococcus is the etiological agent of the disease. Other investigators, however, considered it more likely that the streptococci were merely very important secondary invaders. The objections of the latter group are based on certain important considerations: (a) The streptococcus is an organism which has a widespread distribution and gives rise to a variety of pathological conditions such as abscess formation, cellulitis, erysipelas and septicaemia. (b) Frequently the same individual may have throughout life repeated streptococcus infections, especially true of erysipelas, one attack not seeming to confer immunity against subsequent invasion of the tissues by the same organism; whereas, in contrast to other streptococcus infections, one attack of scarlet fever appears to confer a lifelong immunity. This peculiarity of

scarlet fever might have been explained if it had been possible to prove that there are various strains of streptococci and that the streptococcus concerned in the production of scarlet fever differed specifically from streptococci, causing the various septic processes. However, efforts to separate the scarlatinal streptococcus by biological characters and biochemical reactions from streptococci found in other diseases have failed and to-day still fail. Whatever be their source, streptococci, when grown in fluid or on solid media resemble one another very closely morphologically. Some differences have been discovered by means of the fermentation of the various carbohydrates, but such variations apparently do not bear any specific relationship to a single disease process and have been of little help in determining the etiological significance of the streptococcus in scarlet fever. (c) In addition to this a strong objection was raised by Jochmann (1905). He emphasised especially his failure to find the streptococcus in either the blood or tissues of individuals dying in a few days from malignant forms of the disease. Since, therefore, types of streptococcus indistinguishable from those observed in scarlet fever are found in many pathological conditions, since the quality of the immunity in this disease differs widely in its duration from that in other streptococcus infections, and/

and finally because of Jochmann's contention that the streptococcus is not present in malignant forms of the disease, the conclusion was drawn that the streptococcus cannot be the cause of scarlatina.

An effort to meet these objections has been made by an ever enlarging group of investigators, who believe that the streptococcus is the etiological agent of scarlet fever. The very observation made by Baginsky and Sommerfeld of the constant presence of streptococcus in the throats of all cases of scarlatina, an observation which was later confirmed by others, has done much to counterbalance the inferences drawn by Jochmann's failure to find it in a few cases of fulminant character. Attempts were made, too, to explain the immunity in scarlet fever and to establish the type specificity of the streptococcus associated with scarlet fever. Moser (1902) in Austria reasoned that, if the streptococcus was the cause of scarlatina, a serum for curative purposes might be prepared. He isolated strains of streptococcus from a number of cases of scarlet fever and produced from the horse, after repeated injections with the living streptococci together with the broth in which they had grown, an anti-scarlet fever polyvalent serum. Both the organisms and the culture broth were used so as to get the antigenic value of the organisms as well as of any toxins which might have been developed in the broth. Moser obtained

good therapeutic results by the use of this serum and in the light of more recent knowledge the beneficial action was doubtless due to antitoxic rather than bactericidal properties. There was a drop in temperature and pulse, a diminution of toxaemia, early disappearance of the rash and a shortening of the duration of the disease. Moser was also able to demonstrate that this scarlatinal serum, prepared from horses, agglutinated various strains of scarlatinal streptococci to a titre of 1 in 1000 and over, whereas streptococci from other sources were not specifically agglutinated. Furthermore, Moser and von Pirquet (1902) claimed that serum obtained from scarlet fever convalescents agglutinates the scarlatinal streptococcus to a higher titre than does control serum from other diseases. As a consequence of these observations Moser and Pirquet believed that the streptococcus of scarlatina differs specifically from apparently similar strains isolated from other sources of streptococcal infection.

Later, Savchenko (1905) in Russia went more fully into the matter of the production of an immunising serum. He showed that it contained both specific bactericidal bodies and antitoxin to the streptococcus. He proved, moreover, that the filtrate from the broth in which the culture had grown contained a strong toxin and by inoculating horses with this toxin a

serum which was solely antitoxic, and not antibacterial, could be elaborated. The credit, therefore, for the development of an antitoxic serum for scarlet fever must be given to Moser and Savchenko. Another Russian worker, Gabritchewsky (1906) brought out further interesting facts which indicated the specific relationship of streptococcus to scarlet fever. He took up the work of using a vaccine made from the toxin and the cells of streptococci isolated from scarlatina for the purpose of developing immunity in individuals against scarlet fever. The vaccine was made of bouillon in which streptococci had grown and been killed by heat, and contained 3 per cent by volume of streptococci. Three doses were given subcutaneously at weekly intervals, the dose for children between 2 and 10 years beginning at 0.5 cc. During the process of immunisation certain phenomena occurred which were highly suggestive of the clinical manifestations of scarlet fever. In the majority of cases an area of erythema and swelling, averaging 15 cm. in diameter, developed at the site of injection of the vaccine, appearing in eight to twenty-four hours and lasting about forty-eight hours. In general the erythema was diminished or absent in the subsequent injections. Besides the local reaction, 13 per cent of the children developed general reactions consisting of/

of a rise of temperature of 1°C. or so, accompanied by a fine erythematous rash having the distribution of scarlet fever, which was not followed by desquamation. Some of those inoculated developed a sore throat and strawberry tongue peculiar to the disease, and a few vomited. He found that the second and third injections, although they were two and four times as large as the first rarely produced a rash. This was considered by him as evidence of the rapid development of immunity. Gabritchewsky (1907) later gave further evidence in favour of vaccination. Besides the development of a generalised rash, vomiting, a strawberry tongue and angina in some cases, the additional features of renal irritation in a few and acute nephritis in one case were observed. Moreover, in individuals recovering from the disease or who had had it some years before, local and general reactions were usually absent. Prophylactic immunisation of this kind seemed to diminish the incidence of scarlet fever. Administration also of Moser's anti-scarlatinal serum before inoculation was shown to prevent the development of local and general reactions. Since a scarlatinal streptococcus vaccine, toxin and organisms in this case, was able to produce manifestations of scarlet fever, Gabritchewsky was strongly of the opinion that the streptococcus is the cause of scarlet fever. He thought also that he had/

had lent confirmatory evidence to the growing conception that scarlet fever was a disease similar in its morbid processes to diphtheria. The scarlet fever streptococcus produced its toxins in the throat; these are absorbed into the blood and bring about the rash, fever, and other symptoms. The lowered resistance of the individual allowed the scarlet fever streptococcus and other streptococci to invade the tissues and lead to the so-called complications.

Much other evidence for and against the etiological relationship of the streptococcus to scarlet fever was presented at this time, and the positive seems to outweigh the negative. The greatest difficulty in the way of accepting the streptococcus theory was the impossibility of separating this organism satisfactorily from other streptococci, associated with a great variety of septic conditions. Andrewes and Horder (1906) presented an exhaustive report on the study of streptococci pathogenic to man, in which considerable attention was devoted to the relationship of certain strains with both scarlet and puerperal fever. The results of cultural tests were held to be too conflicting for very definite conclusions, but the evidence went to show that if any particular streptococcus was concerned, it would probably be one of the haemolytic types named "anginosus" as the more likely causative agent, with "pyogenes"/

"pyogenes" as an important, though secondary factor, both having been found in the throats of scarlet fever cases. The joint authors of the report suggested that scarlet fever might be due to: (a) A streptococcal infection primarily, although evidence was not complete to indicate one specific variety of streptococcus. (b) A specific streptococcus, as designated by Klein and Gordon ("scarlatinae") and Kurth ("conglomeratus") within the limits of the "anginosus" group. (c) Some non-streptococcal cause which was ultramicroscopic.

Various investigators took up different lines of attack on the etiological problem and in the resulting confusion of issues Moser's serum and Gabritchewsky's vaccine dropped into disuse. Opinion varied concerning the existence of biologically varying types of streptococcus and two diverging points of view developed, one maintaining the unity of the species as a type, and the other holding that it comprised a group of organisms different from one another in their biological characters. Schottmüller (1903) had already made an important contribution to the discussion by differentiating streptococci into two groups, the differences being based on their action on blood agar plates, one group haemolysing and the other group failing to haemolyse the red blood cells. This significant grouping resulted in the establishment/

establishment of the types now generally recognised as haemolytic and non-haemolytic streptococci. Further classifications were attempted by numerous investigators by biochemical and serological tests with conflicting results.

By the year 1918 the pioneer work of Moser, and of Savchenko and Gabritchowsky was again taken up by American workers and in Germany by Schultz and Charlton. In America, Dochez, Avery and Lancefield (1919) examined a large number of strains of the Streptococcus haemolyticus, obtained from a variety of pathological conditions. They tested them for biological types, like those of the pneumococcus and meningococcus, by agglutination, and protection experiments. The result of their investigation was that there are separate biological types among haemolytic streptococci, just as there are among other apparently closely related groups of microorganisms. More than 68 per cent of the strains investigated comprised six definite distinguishable serological types. Later Dochez and Bliss (1920) studied the biology of Streptococcus haemolyticus obtained from the throats of patients suffering from scarlet fever to see if there were any unity of type of this organism in association to the disease. Bliss found that haemolytic streptococci were present in the throats of all individuals examined early in the

course/

course of scarlet fever, thus confirming the same observation made earlier by Baginsky and Sommerfeld. Immune sera, prepared by the inoculation of rabbits, from the strains of the scarlatinal streptococcus agglutinated 80 per cent of strains recently isolated from scarlatinal throats. On the other hand, agglutinating sera prepared from strains of haemolytic streptococci derived from pathological sources other than scarlet fever, failed to agglutinate specifically the scarlatinal strains. And strains of haemolytic streptococci obtained from such sources as erysipelas, tonsillitis and other septic conditions were not agglutinated by the scarlatinal antistreptococcic sera. This work indicated that the majority of haemolytic streptococci found in association with scarlet fever belong to a specific biological group and could be distinguished from haemolytic streptococci related to other pathological conditions, agreeing with the earlier studies of Moser and von Pirquet on the same subject. Tunnicliff (1920), contemporaneously with Dochez and Bliss, was also engaged, by means of the opsonic and agglutination reaction, in the investigation of haemolytic streptococci obtained from the throats of scarlet fever in its early stages. She concluded that the serum of sheep, immunised against such streptococci, contains opsonins and agglutinins for the haemolytic streptococci obtained from the throat/

throat and complicating lesions early in scarlet fever, but not for haemolytic streptococci obtained from other sources, e.g. erysipelas, measles, diphtheria and the normal throat. The results of her absorption experiments also indicated that the scarlatinal haemolytic streptococcus forms a distinct serological group, scarlatinal streptococci removing the opsonins and agglutinins for these streptococci while there is no such absorption with a haemolytic streptococcus derived from erysipelas.

In this country, somewhat later, Gordon (1921) working on the serological grouping of haemolytic streptococci distinguished the scarlatinal streptococcus as Type IIIv . He found that eighteen strains of this streptococcus were identical in their agglutinative reactions, whilst none of them absorbed the agglutinins from immune sera prepared from other types of haemolytic streptococcus, designated by him as Types I and II. On this evidence Gordon therefore concluded that the streptococci from the throat in scarlatina constitute a group serologically distinct from other varieties of streptococcus pyogenes. Later still, Eagles (1924) compared the serological reactions of haemolytic streptococci from scarlet fever, puerperal fever, erysipelas and other sources, and confirmed the immunological specificity of the scarlatinal group.

On/

On the other hand, in America again, Williams (1924), studying the serological reactions of the scarlatinal streptococci, found only 35 per cent to belong to a single type and she held that a greater variability exists than is suggested by previous workers. Dick and Dick (1924 b) distinguished two strains of scarlatinal streptococci serologically, a mannite and a non-mannite fermenter, and believed that the agglutination reaction is of but little importance in determining the character of the streptococci of scarlet fever. From these observations it would appear, therefore, that the question of the specificity of the streptococcus to scarlet fever was not fully assured and still remained in dispute.

Much evidence had meanwhile been accumulating in favour of the existence in scarlet fever of a soluble circulating toxin, specific in character. Schultz and Charlton (1918) had described the so-called extinction phenomenon, known by their name. They discovered that if 1 cc. of a serum from a normal person or from a patient convalescent from scarlet fever is injected intradermally into the skin of a scarlet fever patient with a bright red rash, there appears at the site of injection a characteristic change. This change begins after about six hours and consists in a complete blanching of the rash several centimetres in diameter. The colour of the blanched/

blanched area is that of normal skin. On the other hand, serum taken from scarlet fever patients during the acute stage of the fever invariably gave negative results. Subsequent investigators, e.g. Henry and Lewis (1925) and Birkhaug (1925) abundantly corroborated the accuracy of this reaction, and it was established that the serum of about 60 per cent of normal adults and of 80 to 100 per cent of convalescent scarlatinal patients possesses the capacity to blanch the rash in an active case of scarlet fever; and that the serum during the active stages of scarlet fever never manifests blanching power. The Schultz-Charlton reaction was first used as a diagnostic test of scarlet fever and the capacity to extinguish the rash was believed to be due to a normal property of human serum, temporarily lost in the acute stage of scarlet fever and regained during convalescence. Mair (1923) however gave the phenomenon a more satisfactory explanation. He published further results and confirmed previous observations but also showed that the serum of some normal persons failed to cause blanching and that the serum before an attack of scarlet fever did not give a positive Schultz-Charlton reaction but during convalescence acquired the power to give a positive test. This disproved the belief that a positive reaction was due to some property of normal human serum which is lost in the acute stages of scarlet/

scarlet fever. He concluded that the reaction was due to the action of an antitoxin on the toxin of scarlet fever. In explaining the phenomenon he came to believe that the rash and other changes in the skin in scarlet fever are due to scarlatinal toxin entering into combination with the tissue cells. Among the affected cells are those contractile elements which exist even in capillary blood vessels and to the function of which the normal tone of the capillaries is due. The toxin causes a loss of tone of the contractile elements of the capillaries which results in the exudative phenomena and erythema prominent in the scarlet fever rash. He supposed that the serum which gives a positive Schultz-Charlton test contains an antitoxin which is able to dislodge and neutralise the toxin fixed in the cells and this restores their normal function over the area injected. He postulated that the causal organism of scarlet fever when discovered should be capable of producing a toxin, and that the immunisation of animals to this toxin should produce an antitoxin capable of producing a positive Schultz-Charlton reaction in man.

Dochez (1924) developed such a serum by an ingenious method of injecting subcutaneously into horses masses of melted nutrient agar and then infiltrating these with increasing doses of scarlatinal streptococci. After nine months the first animal was bled/

bled and the serum tested by Blake, Trash and Lynch (1924). These workers demonstrated that the intradermal injection of the serum into a bright scarlet fever rash causes complete extinction of the rash over an area five to ten centimetres in diameter. The blanching appears in from six to twelve hours following the injection and persists throughout the course of the disease, desquamation being generally absent during convalescence over the blanched area. Even when the serum is diluted several thousand times it is still capable of giving the Schultz-Charlton test. Moreover, injection of a sufficient quantity of the serum intramuscularly in a patient in the exanthematous stage of scarlet fever causes a complete fading of the rash over the whole body in from twelve to twenty-four hours. Moser and Savchenko, using an immune horse serum for therapeutic purposes, had already caused the early disappearance of the scarlet rash, but now the potency of the serum was established by the Schultz-Charlton reaction and a basis provided by which this antitoxic potency could be gauged and standardised. The blanching of the scarlet fever eruption by human convalescent and animal immune serums would thus seem to be a specific local immune reaction to the streptococcus toxin derived from scarlatinal organisms.

From the beginning of the study of scarlet fever efforts/

efforts have been made to produce the disease experimentally in animals without success. This led Andrewes and Horder to point out in 1906 that until scarlet fever had been produced in human beings with a pure culture of streptococcus, no crucial proof had been furnished as to its etiological relationship to scarlet fever. Krumwiede, Nicoll and Pratt (1914) observed an accidental infection in a laboratory worker who sucked into her mouth a mixture of living streptococci containing streptococcus scarlatinae. She developed a typical attack of scarlet fever three days later. Because of the interest aroused by this observation, efforts were made to infect monkeys with the same streptococcus but without success. It remained for the Dicks, following up the work of Savchenko and Gabritchewsky in tracing the cause of scarlet fever, to bring about experimental scarlet fever in the human being.

George and Gladys Dick (1924 e) had already attempted to produce scarlet fever in the usual laboratory animals such as guinea pigs, rabbits and mice by the inoculation of various materials and cultures from scarlet fever, and convinced themselves that animals were comparatively insusceptible to the disease. They (1921) then turned their attention to the human being and made a series of human inoculations with organisms, including the Streptococcus scarlatinae,/

scarlatinae, obtained from the throats of individuals suffering from scarlet fever. Although some of the volunteers experienced sore throat, no instance of scarlet fever developed. Later, the Dicks (1923) repeated their efforts to produce the disease in human volunteers and were successful on Oct. 6, 1923. A haemolytic streptococcus obtained from the infected finger of a nurse suffering from wound scarlatina was used for the purpose of inoculation. Five volunteers were inoculated by swabbing the tonsils and pharynx with cultures of this streptococcus. One developed a definite, though mild, attack of scarlet fever, beginning forty-four hours after inoculation. Next the throats of other five volunteers were swabbed with the Berkfeld V filtrate of a broth culture of the same organism. They remained well and presented neither sore throat nor rash. Subsequent inoculation of four of these persons with living unfiltered cultures of the original streptococcus resulted in the experimental production of another case of scarlet fever. This went to prove that the infected agent was not a filterable virus attached to the strepto-cocci. It was found by them that streptococci isolated from scarlet fever differed from one another in their ability to ferment mannite. The first two cases had been caused by an organism which fermented mannite.

During the year 1923 the Dicks were now investigating the toxin of scarlet fever. In a paper entitled "A Skin Test for Susceptibility to Scarlet Fever" they (1924a) demonstrated the presence of a soluble toxic substance in filtrates from blood broth cultures of the Streptococcus scarlatinae which had caused experimental scarlet fever in man. They ascertained that weak solutions of the toxin may be used in skin tests to determine susceptibility or immunity to scarlet fever. The toxin was first carefully standardised and so diluted (1 in 1000) with sterile salt solution that 0.1 cc. represented a skin test dose. The test consists of an intradermal injection of exactly 0.1 cc. of the skin test dilution on the flexor surface of the forearm. Within about six hours there appears at the site of injection a small circular area of erythema, which increases in size and intensity of colour for from eighteen to thirty-six hours. Frequently the local reaction is accompanied by swelling of the skin. The reaction is observed at the end of twenty-four hours. An area of reddening 2 cm. in diameter indicates marked susceptibility, and 1 cm. some degree of susceptibility to scarlet fever. When a series of normal persons who had not had scarlet fever were tested in this manner, 41.6 per cent showed a positive erythema reaction in the skin, a manifestation resembling the Schick/

Schick test for susceptibility to diphtheria. The remainder who gave a negative reaction were considered to be immune, because of the probable presence of circulating antitoxin in the blood, just as in the case of the diphtheria test. In addition, patients who were recovering from scarlet fever gave negative or only slightly positive skin reactions. In two instances also in which it was possible to observe the test before and after an attack of scarlet fever it was positive before the attack and negative during convalescence owing apparently to the development of immunity. The action of the toxic filtrate on the skin was also shown to be inhibited by convalescent scarlet fever serum mixed with the filtrate or given intramuscularly before the test was made. Next, the Dicks (1924b) were able to produce experimental scarlet fever with the type of streptococcus which did not ferment mannite. They chose two volunteers, one with a negative and one with a positive skin reaction. The two volunteers were inoculated with the same culture of this type of streptococcus. The one with the negative skin test remained well whilst the one with the positive skin test developed scarlet fever. The Dicks therefore considered that they had proved the causal relationship of haemolytic streptococci to scarlet fever. Both their strains were isolated from cases/

cases of scarlatina and they produced experimental scarlet fever; they were isolated again from the experimental disease and again grown in pure cultures. They claimed, therefore, that all of Koch's laws were thus fulfilled.

The Dicks (1924c) next proceeded to develop scarlet fever toxin in relation to preventive active immunisation. They first of all showed that if individuals, who have been proved susceptible to scarlet fever by their test, are injected subcutaneously with larger amounts of the toxin, they exhibit such toxic manifestations of the disease as nausea and vomiting, fever and an erythematous rash. They next showed that these individuals who react positively in the skin can be immunised by repeated graduated doses of the toxin, so that within a relatively short period of time the skin reaction became negative and so that they did not contract scarlet fever on exposure. The Dick's next step was to prepare a scarlet fever antitoxin. Two months after Dochez announced his serum the Dicks (1924d) made a report on the production of an antitoxic serum, obtained by the inoculation of horses with toxin, and standardised according to their method. The therapeutic results of the Dochez and the Dicks serum agreed absolutely with those reported by Moser when observing the effects of his serum. Finally the Dicks (1925a) demonstrated/

demonstrated a procedure for identifying scarlet fever streptococci by the neutralisation of toxin in vitro with the serum of convalescents from scarlet fever and by experimentally produced antitoxic sera.

Zingher (1924) in an extensive study confirmed the observations of the Dicks and extended them somewhat. He pointed out that the Dick reaction is positive in most instances in the early stages of scarlet fever and that it becomes increasingly negative as the disease progresses through convalescence. He also drew a very close analogy between the data obtained with the test and those got with the Schick test in diphtheria. In general, susceptibility is greater in childhood and diminishes in adult life. These and many further studies during the past three years have been productive of an increasing number of observations on the application of the Dick test, not only in America and this country, but in many parts of the world. Chief amongst these are the contributions by Dick and Dick (1925b) and Park (1925) in America; Rozen and Korobicina (1926) in Russia; and Ker, McCartney and McGarrity (1925) and O'Brien, Okell, Harries and Macfarlane (1926) in this country.

These studies indicate that there is present in filtrates from cultures of the haemolytic Streptococcus scarlatinae a soluble toxic substance which bears a specific/

specific relationship to scarlet fever. By means of this substance it is possible to detect in persons susceptibility to scarlet fever and furthermore to demonstrate the development of immunity in patients who are recovering from an attack of this fever. These works accordingly bring further support to the belief that Streptococcus scarlatinae is the etiological agent of scarlet fever.

Nevertheless a certain number of workers have been unable to confirm the claims of the Dicks. Principal amongst these are Italian investigators and they, on the other hand, assert that they have obtained an anaerobic Gram-positive diplococcus in specific relation to scarlet fever. Di Cristina (1921) obtained this organism from the blood of scarlet fever patients by special cultural methods. Other Italian investigators, Caronia and Sindoni (1923) subsequently isolated a similar organism from the naso-pharynx, bone marrow, spleen and desquamating skin of children with scarlet fever. This organism was found to present specific serological reactions with the serum of cases recovered from scarlatina. Inoculation of children with the organism is said to have produced an attenuated form of scarlet fever, whilst prophylactic vaccination with killed cultures prevented the development of scarlet fever among a number/

number of children exposed to the disease. Unfortunately the work of these observers has not been generally verified and has been treated lightly because of the more overwhelming work instituted in America in support of the Streptococcus scarlatinae.

So far in this thesis the possibilities of a protozoan parasite, one of the mysterious ultramicroscopic viruses and Di Cristina's organism have been dismissed as causative agents of scarlet fever. The evidence of a protozoan source was always unconvincing. The whole subject of the so-called filterable viruses is obscure; practically nothing is known of their morphology, little is known of their biology and it is only by carefully controlled work along many lines of investigation that further knowledge can be gained. With regard to Di Cristina's organism it is difficult to determine the actual authenticity of the evidence recorded.

The summary of the data on which has been based the declaration that scarlet fever is due to a specific scarlatinal streptococcus is as follows:-

1. The practically constant presence of Streptococcus haemolyticus in all throats of acute cases of scarlet fever and in many of its secondary manifestations.

2. The experimental production of clinical scarlet fever in human beings (a) by inoculation of this organism/

organism on susceptible throats and (b) by the injection of toxin obtained in the filtrate from a broth culture of the organism.

3. The fact that antistreptococcus horse serum prepared either from the organism or its toxin (a) will give the Schultz-Charlton's reaction, i.e. behave like convalescent scarlatinal serum towards the scarlet rash and (b) clinically ameliorate the symptoms of scarlet fever.

4. The correlation between the streptococcus toxin and susceptibility and immunity to scarlet fever - the Dick Test.

Yet the specificity of the streptococci so constantly associated with scarlet fever is by no means proven finally. Besides the investigations of Gordon, Eagles, Williams, the Dicks and Tunnicliff, already recounted, much work has recently been performed on the serological relationship of scarlatinal strains of streptococci to other streptococci. Amongst the latest reports are those of Smith (1926) and Griffith (1926). Smith has been able to identify 83 per cent of 210 strains of scarlatinal streptococci as Types I and II, whilst Griffith has obtained 3 serological types in 45 per cent of 81 strains studied.
It still appears, therefore, that the etiological separation of the scarlatinal haemolytic streptococci into a group or groups distinct from other haemolytic streptococci/

streptococci is a difficult, if not impossible, task. In a recent paper by O'Brien and Okell (1926), the existence of many points requiring explanation and further study is emphasised, such, for instance, as to whether all scarlet fever toxaemias are due to the same toxin, whether there are different toxins in true scarlet fever, or, in other words, immunologically different types of the disease. They also refer to the suggestion made by Park and Spiegel(1925) that there may be a possible wide antigenic (i.e. anti-body producing) overlapping between the different streptococcci and that the scarlet fever toxic filtrate produced by a single strain is not a single toxin but a group of toxins, so that a person might be immune to one or more of the component toxins of a toxic broth and yet susceptible to others.

The question now remains; Is the so-called Streptococcus scarlatinae the etiological agent of scarlatina? The chain of evidence in its favour is as strong as that in many diseases whose etiology is now accepted without discussion and so strong as to leave little doubt that it is the principal and probably only etiological agent of scarlet fever.

Owing to the vast literature which has accumulated on the subject of scarlet fever, especially within the last few years, it is difficult to deal in detail with all the evidence recorded and to apportion the credit for/

for the development of the present conception (or conceptions) of the disease. The Dicks of Chicago might, however, be fairly singled out for special praise in focussing attention to the "Streptococcic Theory" of Scarlet Fever. Their success in producing experimental scarlet fever in the human being and their discovery of the test which has taken and made their name are triumphs of incalculable worth. On successes such as these depend the intelligent prevention and treatment of disease.

PART II.

I N T R O D U C T I O N.

In the summer of 1924 I was very fortunate in being introduced to the study of the latest experimental work in scarlet fever by that enthusiastic authority on infectious diseases, the late Dr Claude B. Ker of the Edinburgh City Fever Hospital. Six months after Drs George and Gladys Dick described their test for susceptibility to scarlet fever Dr Ker was the first in this country to jump into the field in the investigation of this interesting reaction. In collaboration with Drs McCartney and McGarrity, he carried on this work for six months and a paper on their results was published in the Lancet of Jan. 31st, 1925. Dr McCartney obtained what was considered a reliable toxin for the test from a strain of haemolytic streptococcus isolated from the throat of an acute case of scarlet fever and the test was performed on 883 individuals. Not only did I lend an interested ear to the discussions of these investigators on the problems they set themselves in elaborating the test, but I observed the results of their endeavours.

At the same time I had gained much experience in the application and reading of the Schick test for diphtheria, /

diphtheria, a test on the analogy of which the Dick test was based. The technique of the two tests is identical.

The object of the Dick test known, the technique mastered, the material for the test being obtainable through the kindness of Dr McCartney, and much valuable advice and criticism being forthcoming from Dr W.T. Benson, successor to Dr Ker, the experimental work in connection with this thesis was embarked upon in May 1926 and followed out for the next one and a half years.

Having already had the experience of a year's study of infectious diseases I was struck with the ever occurring difficulties in the diagnosis of scarlet fever. In fact, the greater my knowledge of scarlet fever, the more I had learned to mistrust it. And if there lived in my mind many confusions of issue as to the clinical appearance of scarlet fever, these confusions seemed to be more pronounced in the minds of general practitioners who send their cases to hospital.

A typical case of scarlet fever is easy of recognition; a mild case is often extremely difficult to recognise. A case of scarlatina in which the rash has passed may present many obstacles in the way of diagnosis. A case in which there have been the general/

general symptoms and signs of scarlet fever, with a mere fleeting rash or a rash which has never been detected, may be still more confusing. Again, the similarities of other exanthemata (especially rubella), prodromal rashes (especially chickenpox) and adventitious erythemas to scarlet fever are often intriguing. During convalescence, too, there may be extreme difficulty in confirming a diagnosis of scarlet fever from the evidence of desquamation. Any skin erythema of moderate intensity is followed by pealing of the skin, but in mild cases of scarlet it requires very careful, day to day, search for the evidences of desquamation before a conclusion may be reached. Because of the various types of desquamation encountered I am somewhat sceptical of its value for diagnostic purposes.

Moreover, the importance to me of a diagnosis of scarlet fever, early or late in its course, has become of increasing moment. The gravity of the sequelae of the disease are only now being fully recognised. Scarlet fever infection, although of a mild type, leaves many of its sufferers with damaged health for some years, maybe permanently. Ear, nose and throat complications are frequent and damage to the middle ear may lead to partial or complete deafness. Impairment of the heart is not infrequent, as is also lasting destruction to the structure of the kidneys./

kidneys. The mild infections are therefore also in need of careful observation and diagnosis, if such sequelae are to be forestalled.

It seemed now that some practical application of the Dick's discovery might be made. I determined to investigate for myself the reliability of the test at the same time as using it as a routine measure for the purposes of diagnosis in all doubtful cases of scarlet fever admitted to hospital. Further, as it is frequently necessary to isolate patients who are suddenly taken ill with an erythema and other symptoms suggestive of scarlet fever, but in whom sufficient signs are lacking to make a definite diagnosis, it was hoped that this test might be helpful in arriving at an early diagnosis. This would economise the sideward space reserved in hospital for "observation" cases, particularly at times when the numbers of admissions to hospital were large. It might be so possible in some instances to distinguish between scarlet fever and non-contagious conditions and patients of the latter class might even be lodged in the main fever wards if found to be immune to scarlet fever. The easy application and the rapid appearance of the Dick reaction would be of great clinical value for such projects.

THE DICK TEST.

A. The Toxin.

The Dick test consists in the intradermal injection of 0.1 to 0.2 cc. of a suitable dilution of the soluble toxic filtrate derived from a culture growth of the Streptococcus haemolyticus derived from a typical case of acute scarlet fever. The toxin, Toxin No.1, used was the same as that originally prepared from a scarlatinal strain isolated by Dr McCartney and employed by Ker, McCartney and McGarrity (1925). Latterly, for further supplies of McCartney's Toxin No.1, I have been dependent on Dr McLachlan, through the favour of Professor T.J. Mackie of the Bacteriology Department, Edinburgh University. This toxin diluted to 1 in 1000 and injected in 0.2 cc. amounts had been proved of reliable potency both by its original users and by Joe (1925) and gave results comparable to those of other well-known investigators.

The question of the optimum dosage of the toxin used in the Dick test is momentous. In the case of the Schick test accurate standardisation of diphtheria toxin is possible because of its lethal effect on guinea pigs. On the other hand, laboratory animals are insusceptible to "Dick toxin" and the only present means of standardising it is by observing its behaviour/

behaviour on the human being himself in relation to scarlet fever itself. In the meantime the best criterion of a satisfactory Dick toxin is that of a preparation which when suitably diluted and used in 0.2 cc. doses, causes the largest number of positive reactions in cases of acute scarlet fever and at the same time the largest number of negative reactions in these cases when convalescent.

The method of preparing the Dick toxin used is as follows: The particular Streptococcus scarlatinae (No.1) is grown for 4 to 5 days at 37°C. in a medium consisting of 5 per cent rabbits' blood broth pH 7.6. At the end of that time a film is made from the broth and examined in order to exclude the possibility of contamination. If the streptococcus is in pure culture, the broth is centrifuged in order to deposit organisms, stroma of cells etc., and the clear supernatant fluid is filtered through a Berkefeld V. filter - candle. The resultant filtrate, i.e. Dick toxin, is tested for sterility and stored in the ice-chest. When required, the sterile toxin was made up in a primary dilution of 1 in 100 with sterile normal saline solution, phenol being also added to 0.5 per cent concentration to ensure sterility, and sent out in 10 cm. rubber-stoppered bottles. At hospital the lots were kept in the ice-box and when required for the test diluted to 1 in 1000, 1 cc. of the primary dilution/

dilution being added to 9 cc. of sterile normal saline. This final dilution of Dick toxin is a stable fluid and it was ascertained in the course of its use that it could be kept for several weeks at least without any appreciable diminution in toxic strength being discernible.

B. The Control Test.

For the purpose of the control test the final dilution of 1 in 1000 toxin was heated in a water bath at 100°C. for one hour. The object of the control test is to render the reading of the Dick reaction more infallible by eliminating the portent of occasional pseudo-reactions due to proteins in the test toxin. The boiling process destroys toxin but proteins are not affected to any extent.

C. Method of Applying The Test.

The technique is similar to that of the Schick test. It is imperative to have a good syringe and needle to perform intradermal injections properly. The "Agla" all-glass 1 cc. tuberculin syringe, graduated to 0.05 cc., and the small (half inch) sharp dental needle, No.214, supplied by Messrs Burroughs Wellcome & Co. are very suitable. The syringe has as accurate a fit as syringes go, and only when it is ageing from long use is there any appreciable/

appreciable leak back between the barrel and piston. Any little loss of fluid can be compensated so that the correct dose or very nearly the correct dose is adjudged. The correct dosage is important, more so when a control test is part of the procedure, and especially in the testing of adults in whom pseudo-reactions are more likely to arise. The syringes, of which there are two, one for "test" use suitably marked, and one for "control" use, were sterilised by boiling once a week. In the intervals, before the application of any tests the sterility of the syringes was maintained by washing them through with ether and allowing to dry before use. The needle point was merely wiped on a pledget of cotton wool soaked in ether between each test. The life of the needle was about a hundred injections. The test areas of skin were sterilised by rubbing over with cotton wool soaked in ether. The ether dries quickly and leaves the skin nicely cleaned and prepared for the injection. With this technique no septic inflammation occurred locally at the point of injection.

The site chosen for the injection is the anterior surface of the forearm immediately below the flexure fold of the elbow. One fifth of a cubic centimetre (0.2 cc.) of the 1 in 1000 dilution of toxin is injected intradermally on the left forearm for the test and a similar amount of the heated, inactivated, toxin/

toxin dilution on the right forearm for the control. Great pains were always taken to obtain a satisfactory intradermal injection. Firm traction is applied to the surface of the skin and the point of the needle inserted, almost parallel to the surface of the skin, and in such a way that the point does not penetrate beyond the epidermis and so that the bevel at the point of the canula is actually visible through the superficial epidermal layer. The cuticle is picked up, as it were, on the point of the needle. The fluid is now injected and a white circular bleb or wheal, about 1 cm. in diameter, makes its appearance. The bleb should be sharply defined and its sides should rise almost perpendicularly to the skin surface. The surface of a well-formed wheal is pitted by the little sweat pores in the skin. The small wheal disappears in a few minutes. A moderate degree of resistance to the injection is felt when the needle-point is situated in the correct intradermal position. A great degree of resistance would indicate a position too superficial whilst the absence of resistance would denote that the needle had pierced the sub-cuticle and that the injected fluid was consequently distributed in the subcutaneous tissues and lost for the purposes of the test. In order to obtain accuracy and to render the injection as painless as possible, it should be performed slowly. Great precision/

precision is required if accurate results are to be obtained. All tests were made as early as possible after the admission of doubtful cases of scarlatina to hospital.

D. Method of Observing the Reaction.

A reading of the test was always possible and made in from 12 to 18 hours and the reaction was always observed and finally recorded at the end of 24 hours. Four different reactions were distinguished, namely positive, negative, pseudo-negative and pseudo-positive or rather positive-combined.

Positive Reaction. In the positive reaction nothing develops at the site of the control injection but on the "test" arm a small circular area of erythema appears in five or six hours. This red area increases and reaches its maximum in size and intensity about twenty-four hours after the injection. In the less strongly positive reactions the maximum is reached between eighteen and twenty-four hours. In the most strongly positive reactions superficial inflammatory oedema and slight induration of the skin may be present. Soon after reaching its maximum size and intensity the reaction begins to subside and even the more strongly positive is generally completely faded in 48 to 72 hours. Occasionally after a pronounced reaction a slight pigmentation followed/

followed by a fine superficial scaling of the skin are noticeable a week to ten days after the test.

The variations in the size and intensity of the reactions are wide. As a rule the area is circumscribed, although its margins may shade off into the surrounding skin. Even the faintest discernible blushing of the skin was read as some indication of positivism and all reactions were measured in two diameters by a thin bone centimetre scale. The margin of error in the reading is one in which the personal equation can almost be excluded since this equation is replaced by an observation on a scale. A reading below 10 millimetres in any diameter was not considered a positive reaction. Readings up to 5 cm. in diameter were recorded but the general average size was 2 cm. The various degrees in the intensity of redness ranged from very bright to bright, moderately bright and faint.

Negative Reaction. The negative reaction presents no change at the site of the test and control, the skin remaining unaffected.

Pseudo-Negative Reaction. The clear cut positive and negative reactions are easily read, but pseudo-reactions are often extraordinarily difficult to estimate. The pseudo-reaction usually appears before the true reaction and fades more rapidly. It was left to the twenty-four hours' reading to decide whether/

whether or not the pseudo element was present. The pseudo-negative reaction is read as an area of redness similar in size and appearance at the site of the test and of the control, advancing and subsiding equally.

Positive-Combined Reaction. The positive-combined reaction is greater in area and appears more intensely on the test (left) arm than on the control (right) side.

E. Interpretation of Results.

For the purposes of the Dick test positive reactors are susceptible to scarlet fever, in that they have no antitoxic immunity. Negative reactors are immune to the disease or have developed immunity through the formation of antitoxin in the course of the disease. The pseudo reactions are due to some protein constituents of the test fluid. Pseudo-negative reactors are considered immune to scarlatina. Positive-combined reactors, although sensitive to protein, are susceptible to the malady.

RESULTS WITH THE DICK TEST.

I. Variations in the Dick Test Toxin.

In estimating the reliability of the Dick test the essential difficulty lies in the adoption of a toxin of suitable reactive potency. The ideal skin test dose lies somewhere between a maximum and a minimum and it can only be gauged by a large series of tests on the human skin in relation to susceptibility and immunity to scarlatina. Given then what is considered to be a standard preparation, it would be possible to obtain erroneous readings, a negative reaction in a susceptible person by reducing the quantity injected, and a positive reaction in an immune person by increasing the dose.

(a) Variation in Results by the Use of a Toxin in Different Amounts. The following experiment (Table 1) was made to find out what differences in the readings of the test were likely to arise by the use of different doses.

TABLE 1. Comparison of Dick Results obtained with 0.1 cc. and 0.2 cc. Amounts of the Same Preparation of Toxin (Diluted 1 in 1000).

Amount of toxin injected.	50 scarlet fever patients in 3rd to 5th week of disease.	
	Positive.	Negative.
0.1 cc.	29	21
0.2 cc.	38	12

Of fifty scarlet fever convalescents, twenty-nine cases gave a positive reading with both 0.1 cc. and 0.2 cc. amounts, whilst the results were negative with both amounts in twelve cases. There is therefore a quantitative variation in the Dick test reaction. In this experiment 18 per cent additional positive reactions occurred on the side of the larger dose of this toxin in convalescent cases.

(b) Variation in Results by the Use of Different Toxins. Filtrates obtained from different sources also vary in their toxic content. The variations between such were recorded by my chief, Dr W.T. Benson, and myself (1927) in a paper on "The Dick Test and Active Immunisation against Scarlet Fever". We tested out preparations kindly sent by Dr A.Zingher of New York and by Dr R.A. O'Brien of Messrs Burroughs and Wellcome along with our Edinburgh toxin. The preparations were all of a dilution 1 in 1000 and employed in the same amounts, 0.2 cc. They were tried out simultaneously in the same individuals, cases of acute and convalescent scarlatina and cases non-scarlatinal. The reactions obtained with Zingher's toxin were much more intense and large compared with the other two, and the much higher percentage of positive reactions obtained in the convalescent scarlatinal and non-scarlatinal groups indicated/

indicated that it was a very potent toxin, indeed too potent at the dilution and dose employed to be applicable as a true test of susceptibility in the population of this country. The difference in potency between O'Brien's and our toxin was not so obvious. In fifty cases of acute and fifty cases of convalescent scarlet fever O'Brien's toxin gave, as compared with ours, a higher percentage of positive reactions in both acute and convalescent cases. These percentages were respectively 100 against 98 in acute cases in the 1st to 3rd day of disease - a slight though important difference, and 24 against 14 in convalescent cases in the 14th to 33rd day of disease - a more marked difference. Dr Benson and I agreed to adopt O'Brien's toxin for the purpose of control in our endeavour to gauge success in the production of active immunity in nurses to scarlet fever (by the injection of increasing doses of toxin), since we thought it better to err on the safe side by using a toxin of slightly excessive potency. On the other hand, I decided to stand by the Edinburgh toxin (No.1) for the interests of this thesis, since this toxin appeared to give a reliable enough result in acute cases of scarlet fever and a result more in accordance with what is expected in convalescent scarlet fever.

II. The Dick Test at Different Age Groups.

Apart from the help it might furnish as a diagnostic measure, I applied the Dick test in cases other than scarlet fever. A considerable amount of evidence so accumulated on its value as a means of detecting the susceptibility to scarlet fever of the floating population of the Edinburgh City Hospital. The reactions to the test are set forth in Table 2.

TABLE 2. Percentage of Positive Dick Tests in 1879 Individuals, of Different Ages, not Suffering from Scarlet Fever.

Age period in years.	Total Cases	Dick positive	Dick negative	Percentage of Positive Reactions.
0 - ½	17	2	15	11.8
½ - 1	45	17	28	37.7
1 - 2	130	71	59	54.6
2 - 3	164	99	65	60.3
3 - 4	152	92	60	60.5
4 - 5	137	89	48	65.0
5 - 10	511	283	228	55.4
10 - 15	226	96	130	42.5
15 - 20	183	55	128	30.0
20 - 30	237	76	161	32.1
30 - 40	50	15	35	30.0
40 - 50	19	4	15	21.0
50 - 60	8	0	8	0
Totals	1879	899	980	47.8

For the sake of comparison these results are tabulated (Table 3) alongside those obtained by Ker and coworkers, and by Joe, who all used the same toxin as I did, and by Zingher, who tested the large number of 7,700 normal persons.

TABLE 3./

TABLE 3. Positive Percentage of Dick Reactions, in Age Groups, of Persons not Suffering from Scarlet Fever, Obtained by Different Workers.

Age Period in Years.	Positive Percentage of Dick Reactions.				Positive Percentage of Schick Reactions.
	Table 2. 1879 cases.	Ker & Coworkers (1924) 442 cases	Joe (1925) 634 cases.	Zingher* 7,700 cases.	Ker & McGarrity (1924) 2176 cases.
0 - ½	11.8	0.0	20.0	44.8	15.3
½ - 1	37.7	7.1	53.6	65.3	75.0
1 - 2	54.6	40.0	59.4	71.6	80.9
2 - 3	60.3	67.8	59.8	64.2	82.9
3 - 4	60.5	55.5	60.0	60.5	72.0
4 - 5	65.0	66.6	56.6	48.4	69.3
5 - 10	55.4	58.8	51.3	33.6	58.4
10 - 15	42.5	52.6	40.5	22.8	52.0
15 - 20	30.0	38.4	32.4	16.8	53.5
20 - 30	32.1	48.7	25.4		59.3
30 - 40	30.0	16.6	11.1	14.4	48.6
40 - 50	21.0	50.0	25.0		44.4
50 -	0.0	0.0	-		25.0
Average Percentage.	47.8	51.5	47.9	29.2	61.2

* Quoted by Park, W.H. (1925)

The total number of Cases, 1879, is large enough to allow the deduction of trustworthy percentages. It will be seen that the percentages of positive Dick reactors at different age groups agree fairly closely with those of Ker and even more closely with those of Joe. In fact for the total numbers tested the positive percentage, 47.8, is practically identical with that of Joe, 47.9. Compared with Zingher's of America there is not the same correspondence. The figure, 60.5, for the 3 - 4 age group is identical, but Zingher's are more increasingly positive below that age and more increasingly negative above that age. It would seem therefore that children in this country are not quite so susceptible to scarlet fever and take longer to acquire immunity compared with American children. The figures bear out the fact that the highest percentages occur at ages when scarlet fever has its greatest age-incidence, namely 60 per cent between 2 and 4 years, 65 per cent between 4 and 5 years, and 55 per cent between 5 and 10 years. The percentages, too, present a more even ascending gradient from birth through the first and second quinquennium and descending gradient after the first decade of life. They are also more in accordance with the known age-incidence of scarlet fever, the highest percentage occurring in the 4 to 5 group, compared with those of the others who show the highest

percentage/

percentage in the age-groups 1 to 2 (Zingher), 2 - 3 (Ker & coworkers) and 3 to 4 (Joe).

Ker and McGarrity's results with the Schick test have been included in Table 3. There is a rough similarity between the susceptibility rates of the two diseases, scarlet fever and diphtheria, but it is evident that in the case of diphtheria susceptibility falls most heavily on an earlier age period, 1 to 3, and that immunity is more slow of development.

Judged then by its effect on a non-scarlet fever population, the Dick toxin employed appeared to furnish a reliable index of susceptibility to scarlet fever. But before it could be classed under the category of a standard toxin its behaviour towards the disease itself must be studied.

III. The Dick Test in Relation to Suspicious Cases of Scarlet Fever.

With the object of using the Dick test as an aid to diagnosis and at the same time with a view to scrutinising its validity, the test was applied to all suspicious cases of scarlet fever entering into and arising in hospital. Some of the admissions were labelled "Observation scarlet fever" whilst others sent in as scarlet fever or other disease were considered dubious cases of scarlet fever. The tests were applied as early as possible in the course of the/

the disease and then as far as possible at seven day intervals. When two consecutive negative reactions were obtained, further tests were discontinued.

Altogether 558 individuals came under the ban of suspicion and were tested and observed. To illustrate the difficulty of the diagnosis of scarlet fever Table 4 indicates how perplexing was the outcome.

TABLE 4. Summary of Suspicious Cases of Scarlet Fever, Showing the Numbers Finally Diagnosed as Clinical Cases of Scarlet Fever.

Designation on Admission to Hospital.	Total	Finally Diagnosed as Clinical Scarlet Fever.
Scarlet Fever	307	140
Observation Scarlet Fever	141	78
Diphtheria	64	14
Observation Diphtheria	26	8
Rubella	8	1
Measles	6	1
Whooping Cough	6	Nil
Totals	558	242

From this table it is apparent that only 47 per cent of suspicious cases were finally diagnosed as true cases of scarlet fever. In less than half of the cases notified as scarlet fever was the diagnosis confirmed, whilst just more than half of the cases notified/

notified as "observation scarlet fever" proved to be cases of scarlatina. Of the scarlet fever notifications the greatest confusion existed with regard to tonsillitis and to various erythemas. There were 48 cases of tonsillitis, many with an accompanying erythema of the skin, and 50 cases of various adventitious erythemas including food, drug, sunburn, burn, septic and teething rashes. There were also prodromal rashes in 3 cases of measles and 2 cases of chicken pox. Of the "observation scarlet fever" notifications, tonsillitis (18 cases) and various non-contagious erythemas (17 cases) were again the greatest source of error. There were 14 cases of scarlet fever amongst 64 diphtheria notifications.

With regard to the suspected cases of scarlet fever, the validity of the Dick test was examined in the case of known reactors in relation to susceptibility (Table 5). With this prime object in view it was assumed that the test was fundamentally sound. The results obtained justified the assumption. The usefulness of the test in hospital administration followed as a corollary.

TABLE 5./

TABLE 5. Index of Susceptibility to Scarlet Fever in Relation to Known Reactors to the Dick Test.

Suspicious Cases of Scarlet Fever examined = 558

Number diagnosed as Scarlatina ... = 242

Number diagnosed as Non-Scarlatina .. = 316

Non-Scarlatinal Group = 316	Exposed to Scarlet Fever.		Took Scarlet Fever.
	Directly	Indirectly	
Positive Reactors = 142	16	126	27
Negative Reactors = 174	58	116	Nil

Of the 558 suspicious cases of scarlatina investigated 316 were not diagnosed as instances of the disease. Amongst this class there were 142 positive and 174 negative Dick reactors. No case of scarlet fever arose amongst the group who showed a negative response to the test. Many such were indirectly exposed, whilst 58 were actually directly exposed by being placed in the scarlet fever wards, which as a rule harboured twenty to thirty cases of the disease. Of the number directly exposed, 17 were deliberately placed in the scarlet fever wards and 41 (notified as "scarlet fever") were allowed to remain in these pavilions on ascertaining that the Dick reaction was negative. The fact that not one of the 58 negative reactors contracted scarlet fever on direct exposure was/

was a very gratifying result, supporting the premises that negative Dick reactors are immune to scarlet fever in the first place and that our toxin was giving reliable results with regard to "insusceptibility" in the second place. The test, too, was turned to a profitable use in that the sorely taxed space in hospital, set apart for the observation of doubtful cases of fever, was economised.

Among the 142 positive reactors of the non-scarlatinal group, the positivism of the reaction was maintained on the performance of subsequent tests. And in 27 of these individuals, 16 of whom were directly exposed, scarlet fever was contracted. The onset of the disease in 27 known positive reactors now upheld the reliability and value of the test with respect to "susceptibility". The maintenance of a positive reaction, especially when it preserved equal dimensions and intensity, proved of confirmatory value in the diagnosis of those cases other than scarlet fever. The continuous exhibition of positive reactions at a few days' interval was specially serviceable in the diagnosis of cases of tonsillitis accompanied by erythema, rubellar rashes, and early scarlatiniform serum rashes. Positive results moreover drew attention to those who were susceptible to scarlatina and this knowledge was useful in the control of any outbreak/

outbreak of scarlet fever in non-scarlatinal wards. Firstly, when cross infection had occurred, positive reactors could be isolated in order to prevent a further crop of cases of scarlet fever in the ward concerned. Secondly, all positive reactors could receive prophylactic doses of scarlet fever antitoxin. These measures were resorted to in numerous instances and both by isolation and passive immunisation outbreaks of scarlet fever were successfully subdued. Furthermore, where the test was positive and a patient sickened with symptoms suggestive of scarlet fever, the positivity of the test lent weight to the fact that this patient might be developing scarlet fever and at least emphasised the necessity of his prompt removal from a non-scarlatinal ward.

IV. The Dick Test in Relation to Scarlet Fever.

Counting upon the 242 cases of scarlet fever encountered in the suspected batch and the 27 known positive reactors who took scarlet fever, there were 269 cases, whose response to the Dick test was investigated. From the data recorded it was noted for each individual the earliest day on which the test was positive and also the earliest day of the disease on which it became negative. In a small number, 39, of cases, only one result, either a positive or a negative reaction, could be recorded, for instance where/

where a positive reaction could not be followed up for various reasons, or where a negative reaction occurred in an acute case of the disease. Such single positive and negative results, however, fortunately balanced each other so that for the sake of statistics more reliable results were obtained and accurate percentages deduced for what amounted to 230 individuals. These readings of the test in the acute and convalescent stages of the disease are placed in Table 6.

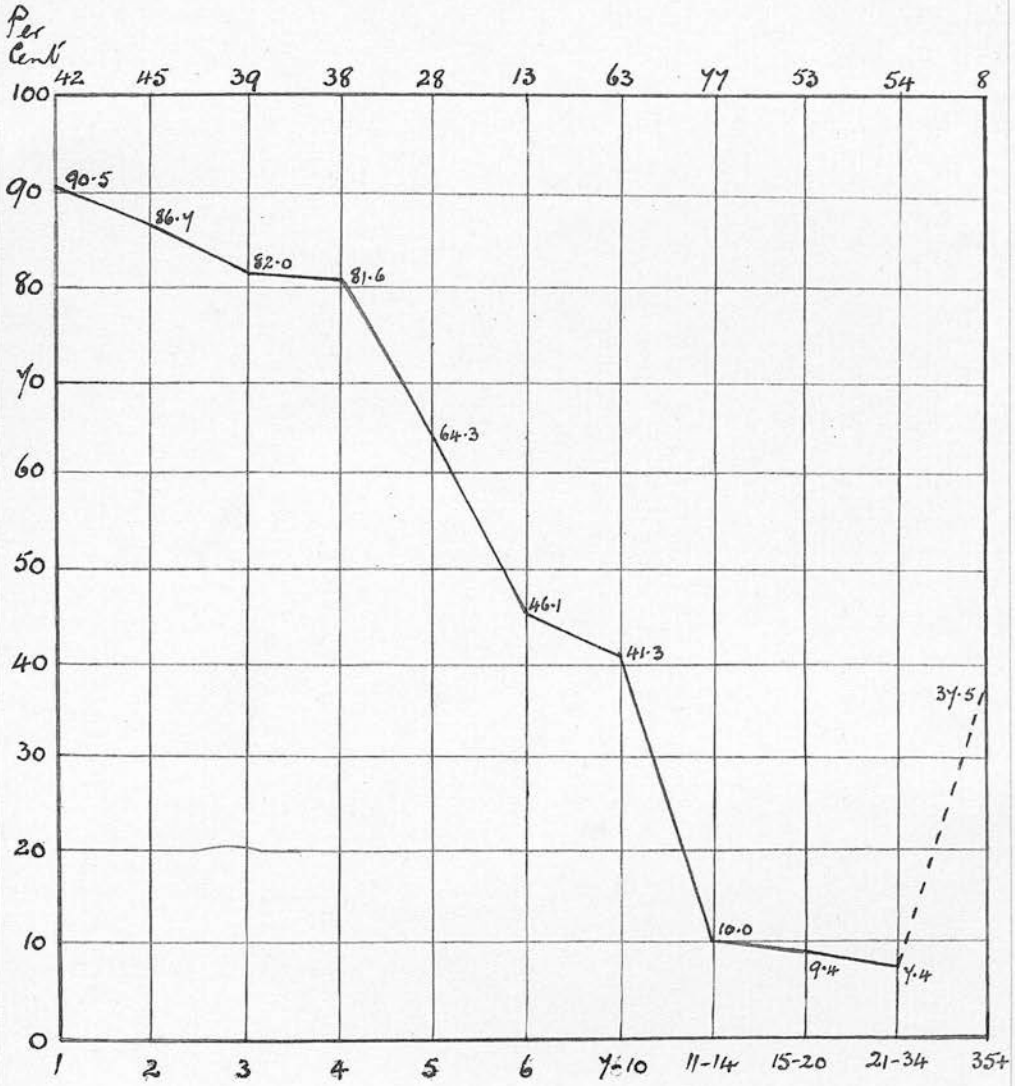
TABLE 6. Results with the Dick Test During the Course of Scarlet Fever.

Days of Disease	Total Tested	Dick Positive	Percentage Dick Positive
1st	42	38	90.5
2nd	45	39	86.7
3rd	39	32	82.0
4th	38	31	81.6
5th	28	18	64.3
6th	13	6	46.1
7th - 10th	63	26	41.3
11th - 14th	77	7	10.0
15th - 20th	53	5	9.4
21st - 34th	54	4	7.4
35th & over	8	3	37.5

As an aid to the appreciation of Table 6 the results are incorporated in graph form, as under.

Graph Showing the Persistence of the Dick Reaction Throughout the Course of Scarlet Fever.

Number of cases.



Days of Illness.

The general conclusion which may be drawn from a glance at the graph is that there occurs, between the acute and convalescent stages of scarlet fever, a definite appreciable fall in the positive percentage rate of Dick reactions. On closer examination the outstanding features of the presence and persistence of the Dick reaction demonstrated by this group of individuals throughout the progress of the disease are:-

1. The positive response in 90.5 per cent of cases on the first day of attack.

2. The persistence of a high rate of positivism, 85.4 per cent, over the first four days of the acute stage.

3. An abrupt steady decline in the positive percentage rate from a high (81.6) to a low (10.0) figure, taking place between the 4th and 14th day of illness.

4. The pronounced declension of positive reactions, 8.4 per cent, from the beginning of the 3rd to the end of the 5th week of disease.

5. A high percentage residue of persistent positive reactions, in a small number of cases, in late convalescence.

Apart from any disquieting points which these data might raise, much general information was gleaned which could avail in the diagnosis of scarlet fever. When a positive reaction gave place to a negative reaction in the course of the disease conclusive evidence of scarlet fever had been obtained. With mild cases of scarlet fever it had often been necessary to wait for desquamation or other signs to confirm the diagnosis. When a positive reaction was replaced later by a negative reaction scarlatina was proved before corroborative clinical evidence was forthcoming. A negative Dick reaction during the first few days of the disease made the diagnosis doubtful. A strongly positive reaction occurring four days after the onset of the disease was against the correctness of the diagnosis since the reaction became rapidly negative after the fourth day. Aside from clinical evidence to the contrary, the persistence of a positive reaction two weeks or more after the fading of a rash would indicate that the patient did not have scarlet fever.

Many of the features presented by the results obtained with the Dick test in relation to scarlet fever are worthy of fuller consideration.

A./

A. Occurrence of Negative Reactions in Acute Cases of Scarlet Fever.

A valid preparation of Dick toxin should furnish 100 per cent positive skin reactions at the onset of the disease. Therein lies the acid test of the Dick reaction. It will be observed that the graph falls short of this ideal. Principally what has to be explained is the occurrence of a relatively low percentage (85.4) of positive reactions in the first four days of the disease and a fortiori the occurrence of four negative results in forty-eight persons tested on the first day of the disease.

What is the reason of these discrepancies? In the review of the literature on the etiology of scarlet fever the strongest evidence was submitted that the haemolytic Streptococcus scarlatinae was the causal factor of the disease. Whilst maintaining the case for Streptococcus scarlatinae let us look for causes to which aberrant results might be attributed.

The most feasible explanation that a negative skin test is possible in the acute stage of the disease is that the toxin employed was not sufficiently potent. Since serological investigations have failed not only to discriminate between scarlatinal strains but also to differentiate such clearly from non-scarlatinal strains it would appear that probably

the only experimental criterion of a scarlatinal strain lies in its capacity to produce a toxin which demonstrates specific toxic properties towards cases of scarlet fever. Our toxin certainly demonstrated its specificity in relation to known positive and negative reactors since positive reactors took scarlet fever and negative reactors did not. Yet it may be that it was employed in too weak a concentration to obtain positive reactions in every case of acute scarlet fever. But since the same toxin indicated susceptibility and non-susceptibility to the disease and since it was strong enough to provide a fair number of persistent positive reactions in the convalescent stage of the disease, there could not have been a wide margin of potency between the ideal and our toxin.

Another explanation which straightway protrudes itself is that a faulty technique was employed. However, to guard against possible aberrant negative reactions every precaution was taken. In the performance of a large number of tests it was apparent that there is a great variation in the amount of natural antitoxin in different individuals, the degree of reaction to the toxin being taken as an index of the degree of susceptibility. In an endeavour to bring even mildly susceptible individuals into their proper group as positive reactors careful measures

were/

were taken. The skin test dose was accurately given. Tests were applied in groups with fresh toxin so that a series of controls were always at hand for each observation and for each lot of toxin used. Sometimes there is a difficulty in the reading of the test where a resultant positive erythema has become merged into a bright scarlet fever rash. A positive might be read as a negative reaction when it does not stand out by contrast from the surrounding rash. In such cases close observation is necessary and by applying pressure over the test area by rubbing it with the forefinger the reaction can be made to stand out more clearly. In the cases in point, however, the scantiness of the rash precluded any difficulty of reading the test.

In searching further afield to explain the occurrence of negative responses at the onset of the disease the evidence afforded by Bristol (1923) that scarlet fever is a reaction of hypersensitiveness to streptococcus protein merits attention. Bristol demonstrated that virulent haemolytic streptococci were present in practically every scarlet fever throat, but not so generally present in other diseases or normal throats. By the use of cutaneous tests with streptococcus protein he obtained about 50 per cent positive reactions in normal persons, with or without a history of scarlet fever. On the other hand the

same test applied to persons in the early stages of scarlet fever gave uniformly negative results. From this it was concluded that while a fair number of normal persons are hypersensitive to this particular bacterial protein, individuals with active scarlet fever apparently are in a state of desensitisation. On these findings he suggested that scarlet fever is a reaction of specific hypersensitiveness to streptococcus protein, and that it is a compound condition involving primarily a local streptococcic infection, usually of the throat, and secondarily a streptococcus protein intoxication in those who are sensitive. In support of this theory, that scarlet fever is an allergic protein phenomenon, it might be added that an eosinophilia occurs at the time of the rash and that the Dick test is like a pseudo Schick test in time of appearance and disappearance and also that Dick toxin is very thermostable and unlike Schick toxin which is excessively labile. It is obvious, however, that the negative Dick reactions in early scarlet fever are not to be explained on any such hypothesis as this, since if the Dick toxin is of the same nature as the protein described by Bristol and that the patient in the early stages of scarlet fever is in a state of desensitisation, negative results should be uniformly and not sporadically obtained.

Consideration/

Consideration might also be given to the hypothesis of Park and Spiegel (1925) that the scarlet fever toxin is a complex substance. They suggested that the toxic filtrate produced by a single strain is not a single toxin but a group of toxins and that a person might be immune to one or more component toxins of the filtrate and yet be susceptible to others. It is conceivable that a person might not react to all of the constituent toxins in a particular toxic filtrate and yet be susceptible to scarlet fever or actually in its grip. In other words it may be that whilst the toxin used by us was specific for the majority of cases it was not specific for all cases. Still the negative reaction in most of the convalescents points to a single toxin, as in the case of diphtheria.

Although such a zealous worker as Zingher(1924) obtained 100 per cent positive Dick reactions in 141 cases of scarlet fever in the first five days of the disease, other investigators have not obtained this maximum result. Ker and coworkers (1925) obtained 73.9 per cent positive reactions in the first three days of the disease, Joe (1925) 95.1 per cent and Silcock (1925) 68.8 per cent in the first five days of the disease, and Rosen and Korabicina (1925) 82.4 per cent on the second and third days. Our figure, 85.4 per cent over the first four days of the illness offers a favourable comparison.

B. Occurrence of Positive Reactions in Convalescence.

During the third, fourth and fifth weeks of the disease 8.4 per cent positive Dick tests were recorded. This figure is certainly not in excess of that quoted by other observers over this period. Having already questioned the strength of the toxin by suggesting that it might not have been strong enough to evoke positive reactions in all acute cases it would not now be a fair argument to propose that the toxin was too strong in that it maintained positive reactions in convalescence. The variations in time that patients take to develop a negative Dick reaction may be due to differences in their susceptibility preceding an attack of scarlet fever, in the amount of toxin absorbed from the throat and in individual powers of formation of antitoxin. When, therefore, the Dick test remains positive in convalescence, even in patients who desquamate freely, it would appear due to the fact that the patient does not develop sufficient antitoxin to affect and neutralise the toxin used in the test. He might therefore still be susceptible to the disease. This again might conceivably be due to the fact that a person may succumb to different strains of the specific haemolytic streptococcus. First he may suffer from the disease owing to infection by a particular strain of the organism/

organism and its accompanying toxaemia. Because the toxin used in the test might be derived from a different strain of the streptococcus the patient might react to it throughout the course of his first attack and still be liable to a second infection by another specific streptococcus.

Second attacks of scarlet fever are not unknown and we were fortunate to meet the following explicit example. A boy, aged 5½, passed through what proved to be clinically a definite attack of scarlet fever. He was still Dick positive on his 33rd day of disease and was discharged from hospital a few days later. Twelve months afterwards this boy was readmitted to hospital again with scarlet fever. The second attack was typical and the Dick test, positive at the fourth day of the illness, became negative at the twentieth day. As the test toxin used against both attacks of the disease was the same and as the test became negative during the second attack it would appear that sufficient immunity to the disease was not developed by the original attack.

The persistence of a positive reaction might also explain the appearance of a relapse in the course of convalescence. In support of this proposition three cases of relapse were noted in persistent positive Dick reactors, occurring one on the 28th., one on the 29th and one on the 33rd day of disease.

In/

In every case the typical desquamation of scarlet fever had occurred and the Dick reaction was still positive up to the time of the repetition of the original disease. The Dick reaction finally became negative in all cases.

It will be observed that even after five weeks had elapsed there were yet three positive reactors out of eight persons tested, representing a percentage of 37.5. This percentage, worked out for a small number of cases, gives an entirely erroneous idea of the numbers of positive reactors likely to occur in a large number of late convalescents and for this reason the graph, unscientific as it may be, is finished off as a dotted line. There was also some doubt as to the diagnosis. The disease in all three cases was of a mild nature, the rash evanescent, and desquamation inconclusive.

C. Occurrence of Pseudo-reactions.

In the series tested pseudo-reactions were encountered in 4 per cent of cases. A pseudo-reaction may be an allergic phenomenon due to hypersensitiveness to the autolysed protein of the Streptococcus scarlatinae or to the extraneous proteins of the culture filtrate used for the test. Zingher (1925) is of the opinion that the pseudo-reaction is due to sensitiveness to extraneous proteins. He has stated/

stated that pseudo-negative reactors have antitoxic properties in their blood serum as found in the case of negative reactors and are immune to scarlet fever whilst positive-combined reactors have no such anti-toxin and are susceptible to scarlet fever.

It was noticed that pseudo-reactions did not persist so long as positive reactions, and were not constant in their appearance. They occurred more with one batch of test material than with another. They also varied in the same individual when using the same test toxin. Sometimes a flat negative reaction was followed by a pseudo-negative or vice versa, or a frank positive reaction by a combined positive or vice versa. The occurrence of only a small percentage of pseudo reactions, their short duration and their variations in sequence of appear-ance might be sufficient grounds for advocating the abolishment of the routine control test with heated toxin.

D. Dick Reactions of Persons Giving a Previous History of Scarlet Fever.

Amongst the 242 cases of scarlet fever considered, 44 or 18.1 per cent gave a history of having already had scarlet fever. Not all of the histories could be relied on but there was fair evidence on the whole as to previous attacks of the disease. Of these 44 cases

of/

of previous scarlatina, 17 proved now to be true cases of the disease. Of the remaining 27 only 4 were Dick positive. In 44 cases who were supposed to have had scarlet fever there were therefore 21 or 47.7 per cent who were shown by the Dick test to be still susceptible to the disease whilst 17 or 38.6 per cent had actually taken the disease for a second time. The number of positive reactors occurring in persons with a history of previous scarlet fever and the number of these presenting a second attack of the disease are both large. Nevertheless large percentages of positive Dick reactions in persons who were deemed to have been formerly ill with scarlet fever have also been given by various investigators. Rosen and others (1925) found 63 out of 179 or 35.2 per cent still positive reactors and Okell and Parish (1925) on testing 20 medical students with previous scarlet fever obtained as many as 65 per cent positive reactors.

The continued positive reaction in persons who have had scarlet fever would again bring us back to the supposition already stated. It again seems to indicate that there may be more than one toxin produced by the haemolytic streptococcus associated with scarlatina. If only a single toxin were produced by different strains of the causal agent, only one type of antitoxic antibody would develop during the disease and/

and all scarlet fever patients after the disease would show a negative Dick reaction to the same toxin. Such considerations would indicate that in scarlet fever we are dealing with a variety of clinical entities which are classed together because of the lack of more differential criteria than symptomatic clinical signs.

E. Appearances of Old Positive Dick Reactions During the Acute Stage of Scarlet Fever.

The appearances of old positive Dick reactions were observed in the following interesting case. A girl, aged 16, admitted to hospital as a case of diphtheria was isolated in a side-room adjoining a scarlet fever pavilion. The fauces and palate were congested and the tonsils speckled with points of exudate. The tongue was thickly furred, a scarlatiniform rash covered the body and limbs and there were petechiae at the elbow folds. The throat swabs were negative to the bacillus of diphtheria. The tongue never pealed and desquamation did not occur. On clinical evidence and because bright positive Dick reactions were obtained on the first and fourteenth day of her illness she was discharged from hospital with a diagnosis of tonsillitis accompanied by erythema. On the day of discharge she sickened to scarlet fever and was readmitted to hospital the next day, /

day, now in her second day of a typical attack of the disease. To simplify matters the appearances of the old Dick reactions are shown in the accompanying table.

TABLE 7.

Illness	Day of Disease	Dick Reaction. Size in millimetres.	Appearances of Old Dick Reactions.
Tonsillitis	1st (1)	Positive 22 x 20	-
	14th (2)	Positive 27 x 15	(1) Slight discoloration and superficial desquamation.
Discharged	19th	Took Scarlet Fever.	
Readmitted	20th	Now in 2nd day of Scarlet Fever	
Scarlet Fever.	2nd	Positive 24 x 21	(1) Central blanched area, 15 x 12 mm., with peripheral area of erythema extending outwards to 37 x 22 mm. (2) Erythematous area, 25 x 22 mm.
	12th	Negative	-

It will be seen that the first Dick test appeared twenty days later as a blanched area surrounded by a sharply defined ring of erythema, which was much more intense than the scarlet rash on which it was superimposed and also that the second Dick test had reappeared seven days later as an intensified erythematous area distinguishable from the surrounding eruption. An appearance similar to that noticed in relation to the first Dick test has been cited by Zingher (1924).

In/

In a subject who was given the test one week before the onset of the disease he noticed a blanched area, the rash sparing the region injected, and this area surrounded by a definite ring of redness which stood out on the scarlet fever rash. He suggests that the blanched area is probably due to the fact that the streptococcus toxin injected induces an extinction of the scarlet fever rash through the development of a local cellular immunity. At the same time the ring of intensified redness bordering the pale area is probably caused by the interaction between streptococcus toxin and the cells which were sensitised rather than protected by a minute amount of antitoxin within their substance. In the case of our second test no blanched area was visible and it would seem therefore that a process of sensitisation takes place before local immunity is developed. Brown (1925) noticed the reappearance of an erythematous area at the site of recent Dick tests in cases developing scarlet fever, and he considered the phenomenon as confirmatory of a diagnosis of scarlet fever. On the other hand Ferry (1926) and Toomey (1926) have called attention to a reappearance of the reaction at the site of a previous Dick test coincident with the appearance of a measles rash. In such instances it is possible that a modified Arthus phenomenon was represented.

OTHER OBSERVATIONS IN RELATION TO THE ETIOLOGY OF SCARLET FEVER

Concurrently with the work carried out on the Dick test many interesting cognate points arising out of it were investigated. These observations and a brief account of two interesting cases with a bearing on the etiology of scarlet fever are added.

1. Passive Immunisation to Scarlet Fever with Antitoxic Serum.

For the purpose of testing out the antitoxic strength of antiscarlatinal serum, supplied by Burroughs & Wellcome, the effect on the Dick test was observed. Seventeen positive Dick reactors were selected and given intramuscularly 10 cc. of serum, six different batches (denoted "SA") being used. Dick tests were applied at 24 and 72 hours after injection of serum and again 7 and 10 days after. The results of the Dick tests are shown in Table 8.

TABLE 8./

TABLE 8. Passive Immunity to Scarlet Fever with Antitoxic Sera (10 cc. injected intramuscularly).

Results of Dick Tests on Known Positive Reactors.

Serum(SA) Batch.	No. of Cases	Hours. 24 Pos.	24 Neg.	72 Pos.	72 Neg.	Days. 7 Pos.	7 Neg.	10 Pos.	10 Neg.
1.	3	0	3	0	3	1	2	1	2
2.	2	0	2	-	-	0	2	0	2
3.	4	0	4	-	-	2	2	2	2
4.	4	2	2	0	4	1	3	2	2
5.	4	1	3	0	4	3	1	4	0
Totals	17	3	14	-	-	7	10	9	8

Fourteen out of the seventeen cases will be observed to have been rendered Dick negative at the end of 24 hours from the time of receiving antitoxin, whilst the three who were still Dick positive at 24 hours became negative at 72 hours. Seven cases had again become positive at the end of 7 days and nine after a lapse of 10 days.

Using such sera it would seem possible therefore to prevent scarlet fever infection in the majority of susceptible contacts provided that it is given immediately on exposure. The serum would seem to tide contacts over the first three days of exposure, which corresponds to the usual incubation period of scarlet fever. Many known positive Dick reactors who were contacts/

contacts with scarlet fever were given antitoxic scarlatinal serum and none of these developed scarlet fever.

2. The Schultz-Charlton Reaction,

Many Schultz-Charlton tests were applied with Dochez, Dick, and Burroughs & Wellcome anti-scarlatinal serum, and with the serum of convalescent scarlet fever patients in the fourth week of disease. It was found that positive results, extinction of the rash, were to be expected in scarlet fever (always provided that the test was applied on a well-formed rash and before it was beginning to fade) but not in rubella, measles, erysipelas, and scarlatiniform serum and other rashes. The test was accordingly specific for scarlet fever. It could therefore be used to confirm a diagnosis of the disease but was not so useful in making a diagnosis since once a good scarlatiniform rash is present its recognition as a concomitant of scarlet fever is not such a difficult matter.

3. Possible Case of Scarlet Fever Arising from Laboratory Manipulations with Streptococcus Scarlatinae.

On 15th and 16th June 1925 the patient, a Doctor in the ~~Pathology~~ Bacteriology Department of the University of Edinburgh, was engaged in the preparation of toxin from/

from haemolytic streptococci obtained from the throats of scarlet fever patients. On 18th June he experienced headache and sore throat, and on 19th June a typical scarlet fever attack was evident. Curiously enough, one of his associates had swabbed his throat on 14th June and found that streptococcus haemolyticus was not one of its inhabitants. As the patient was not aware of having exposed himself to scarlet fever it is possible that he infected himself whilst working with material containing the haemolytic streptococcus. Krumwiede and others (1914) reported evidence of the causal relationship of the streptococcus haemolyticus because of the development of scarlet fever in a laboratory assistant. This worker accidentally inoculated her throat by the swallowing of a culture containing several strains of streptococci including a scarlet fever strain.

4. Possible Case of Scarlet Fever Following a Throat Operation.

A girl, aged 13, had her tonsils and adenoids removed in a diphtheria ward where she had not been exposed to scarlet fever. The surgeon who operated had come directly from a scarlet fever ward where he had been performing a few tonsillectomies. The instruments used on the girl were the same as had been/

been employed on the scarlet fever patients. All the usual aseptic precautions were taken. Two days after her operation the girl took scarlet fever.

The implication is that the girl was infected by the virus of scarlet fever either by the instruments used for the throat operation or by the surgeon himself. Lovett (1926) quotes a case in which it was reasonable to presume that infection had been carried by the operator or his instruments. Another possibility is that the girl may have been harbouring the organisms in her throat and was able to resist their invasion until the devitalisation of the throat tissues allowed them to assert infective activity. Less probably, since the girl was not exposed to any known cases of scarlet fever, the open wound may have facilitated the entry of organisms from another person, a "carrier" of infection.

C O N C L U S I O N S.

(1) A toxic filtrate obtained from the haemolytic streptococcus associated with an acute case of scarlet fever was used intradermally in a dilution of 1 in 1000 and in 0.2 cc. amounts as the skin test dose for the purpose of the Dick test. The reaction depended on the quantity of toxin injected and on the particular toxin, deemed specific, employed. The standardisation of a selected toxin is a difficult matter and can only be estimated after a large number of tests have been made in relation to susceptibility and non-susceptibility to scarlet fever.

(2) The toxin adopted and used in testing 1879 persons not suffering from scarlet fever indicated a susceptibility rate just ahead in time of the known age-incidence of the disease. It yielded a high percentage positive rate in the early years of life, the highest incidence, 65 per cent, falling on the 4 to 5 age period. This shows that if the production of active immunity to scarlet fever is adopted as a general preventive measure, in the same way as has been in the case of diphtheria, it should be carried out in the under-school-age period. The average susceptibility/

susceptibility rate for all age periods was 47.8 per cent.

(3) The Dick test determined susceptibility or immunity to scarlet fever. Twenty-seven persons who previously gave positive reactions to the test and were presumably susceptible to scarlet fever contracted the disease whilst not one of fifty-eight persons who were negative to the test took scarlet fever on direct exposure.

(4) In the large majority, 85.4 per cent, of 269 individuals suffering from scarlet fever the Dick test was positive in the first four days of the disease and became negative as convalescence advanced. Only 8.4 per cent gave positive reactions from the beginning of the third to the end of the fifth week. It is frankly admitted that negative reactions have occurred in acute cases and positive reactions in late convalescent cases, and while certain suggestions may be made to account for these, an adequate explanation of such apparent anomalies is not yet forthcoming.

(5) On the whole the results obtained with the Dick test bore a definite relationship to immunity to scarlet fever. They agreed with those obtained by various investigators and were in support of the claim that the Dick test is a valid/

valid one and pari passu that the haemolytic "Streptococcus scarlatinae" is most probably the etiological agent of scarlet fever.

(6) The Dick test affords valuable corroborative evidence on which to base a diagnosis of scarlet fever and may even be regarded as the deciding factor in those cases where the clinical evidence is of a doubtful or conflicting nature. The test was also turned to account in the administrative supervision of the clinical side of the hospital. The practical applications which the test may furnish as a diagnostic weapon and at the same time as a useful measure in hospital administration may be summarised as follows:

(a) A negative Dick test in the first four days of a disease, or a strongly positive Dick test after the fourth day, and more especially after the fourteenth day of a disease, were testimony that the disease was not scarlet fever unless clinical evidence was to the contrary.

(b) A negative reading of the test, however, in the first four days of a disease simulating scarlet fever meant that the diagnosis of scarlatina would have to be withheld until verified later by clinical signs alone.

(c)/

(c) The possibility of an early interpretation of the reaction was of great clinical value. This was specially useful in providing a ready means of preventing exposure of positive Dick reactors to scarlet fever by too hasty an admission to scarlet fever wards. Once exposed to scarlet fever positive reactors could be isolated or could receive prophylactic doses of scarlet fever antitoxin within a day of the application of the test.

(d) Negative Dick reactors could be placed or allowed to remain in scarlet fever pavilions without much fear of their taking scarlatina.

(e) Cases in whom the diagnosis was in doubt and who by reason of single or repeated Dick tests were considered non-scarlatinal need not be kept in hospital for the usual four to five weeks' supervision. Dick negative reactors who came into actual contact with scarlet fever could be sent home with equanimity.

(f) The test enables one to discriminate in the selection of a nursing staff for scarlet fever pavilions and to ensure that only non-susceptibles shall be so employed. Susceptible nurses could be prepared for scarlet fever duty by a process of active immunisation which is now available and which is actually in routine use in some fever hospitals.

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